DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/31/2009 has been entered.

2. Claims 1, 4-7, 9, 13, 20-23, 46-47, 50, 52-62, and 66-74 are pending for examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 103

4. The rejection of claims 46-47, 62, and 69-72 under 35 USC 103(a) is withdrawn in response to Applicant's arguments.

5. Claims 1, 4-7, 9, 13, 20-23, 50, 52-61, and 66-68, and 73-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shoshan et al. (WO0210449) in view of Bennett et al. US Patent No. 6172216, and Wengel et al., for the reasons of record.

6. Applicant's arguments filed 03-31-09 have been fully considered but they are not persuasive. Applicants argued that Shoshan et al. offers no reason to select SEQ ID NO: 28624 for designing antisense, and that the Examiner has failed to provide any

reason why it is obvious to select this particular sequence out of the 32,337 sequences disclosed, or to select the antisense oligonucleotides of the pending claims out of the literally tens of millions of potential antisense that could be designed based on Shoshan.

7. Applicants further argued that the Examiner is engaging in impermissible hindsight analysis, and that without the benefit of Applicant's disclosure of SEQ ID NO: 19 or claimed compounds, one of skill in the art is faced with the disclosure of 32,337 potential templates to make antisense. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

8. Applicants further argued that decision in *Takeda Chem. Indust., Ltd. V. Alphapharm Pty., Ltd.,* supports Applicant's assertion of non-obviousness of the claimed invention. In particular Applicants argued that Takeda is directly applicable to the instant case. "[L]ike Takeda' the Shoshan reference discloses thousands of starting points for one of skill in the art to investigate new compounds, "any one of which could have been selected" for further investigation. The Examiner's obviousness argument, like Alphapharm's, requires that a single starting compound, SEQ ID NO: 28624, be selected from the long list of disclosed compounds. As was the case in Takeda, the

starting compound is expressly disclosed in the cited reference. However, unlike Alphapharm, the Examiner has not even attempted to provide a reason one of skill in the art would select the particular starting compound, instead merely relying on the fact that it is expressly disclosed.

9. In regards to the Takeda decision, the facts of the instant case differ to the extent that in the Takeda case the court decided that there was not “basis to select “compound b” as the starting compound for further modification out of all of the disclosed compounds, in the instant case there is clear suggestion from the Shoshan et al. reference that all members of the oligonucleotide families described in the reference are all equivalently useful as targets to design antisense compounds. Moreover, plaintiff’s application in the Takeda case disclosed "hundreds of millions” of TZD compounds to select from, in comparison to the 32,337 oligonucleotides disclosed in Shoshan et al.

10. Furthermore, the decision of Takeda was based upon a distinct set of facts. For example, the prosecution of Takeda included prior art that actually taught away from the selection of compound b as a start compound, there is no such evidence provided in the instant case as to why the person of ordinary skill in the art would not have selected SEQ ID NO: 28624 as a start compound. Moreover, the scope of the instant claims read on an exponential number of potential compounds that are 12 to 50 nucleobases in length and comprise only 8-contiguous nucleobases of SEQ ID NO: 19. As further discussed below, the Examiner agrees that specifically selecting SEQ ID NO: 19 from among the nucleobases of SEQ ID NO: 28624 of Shoshan et al. is not obvious in light of the unexpected properties described below. However, the superior properties of SEQ

ID NO: 19 are not representative of the full scope of compounds encompassed by the instant claims.

11. Furthermore, Applicants argued that in Example 15, Table 1 of the specification, SEQ ID NO: 19 shows 79% inhibition of Human Growth Hormone Receptor expression *in vitro.* According to Applicants this result is "clearly unexpected in view of the cited references."

12. The Examiner agrees with Applicants that antisense compounds of at least 20 nucleobases in length which comprise or consist of SEQ ID NO: 19, and is 100% complementary to SEQ ID NO: 4, and having 79% inhibition are non-obvious. However, Applicant's showing is not commensurate in scope with the claims and does not provide sufficient evidence to render non-obvious the full scope of the claimed genus of compounds. For example, the SEQ ID NO: 20, which comprises a 15 nucleobase contiguous stretch of SEQ ID: 19, has only 52% inhibition as measured in the same conditions as SEQ ID NO: 19. This marked reduction in inhibition by reducing the number of contiguous base pairs shared with SEQ ID NO: 19 does not suggest that further reducing the number of contiguous nucleobases from 15 to 8 would yield a compound with comparable inhibition with SEQ ID NO: 19. On the contrary, one of ordinary skill in the art would have expected that by reducing the number of contiguous base pairs shared with SEQ ID NO: 19 from 15 to 8, would actually result in a further reduction in activity. Therefore, Applicant's reliance upon the data set forth in Table 1 is not sufficient to render non-obvious the full scope of the compounds set forth

in the instant claims which encompasses compounds of 12 to 50 which comprise an at least 8 nucleobase portion of SEQ ID NO: 19.

13. As stated in the prior Office Action, contrary to Applicant's assertions, although Shoshan et al. generically states that using known techniques, "an antisense RNA based upon *the oligonucleotides of the present* invention can be employed to inhibit or prevent translation of an mRNA at the cellular level," there is no rationale why this statement would not be readily applicable to an explicitly described species of the oligonucleotides of Shoshan et al., namely SEQ ID NO: 28624. The oligonucleotides of Shoshan et al. are individually described by sequence in the sequence listing attached to the reference.

14. Additionally, it is noted that the Shoshan et al. reference was applied as a 103 reference in view of Bennett et al. and Wengel et al. However, Applicants continue to argue the deficiencies of Shoshan et al. individually as not teaching the claimed invention.

15. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

16. Furthermore, in contrast to Applicant's assertions, since the target sequence of Shoshan et al. was disclosed in the prior art, wherein the target sequence is only 65 base pairs in length, it would have been within the level of the ordinary skilled artisan at

the time of the instant invention, following the teachings of Bennett et al. and Wengel et al. to design antisense compounds of 12 to 50 base pairs in length targeting the 65 base pair oligonucleotide sequence of Shoshan et al. One of ordinary skill in the art would have been motivated to design the compounds of the instant invention, since the target sequence of Shoshan et al. is explicitly disclosed, and the number of potential members of the genus of antisense compounds of 12 to 50 nucleotides comprising an 8-nucleobase contiguous stretch of the 65 nucleotides of SEQ ID NO: 28624 can be readily envisioned. Moreover, due to the small number of nucleotides set forth in SEQ ID NO: 28624, and the fact that Bennett et al. teach that antisense oligonucleotides are preferably 20 base pairs in length, compounds of comprising an at least 8-nucleobase portion of SEQ ID NO: 19 of the instant invention could be immediately envisioned due to the limited number of possible 20 base pair non-overlapping antisense oligonucleotides that could be designed based upon a sequence of only 65 base pairs.

17. Additionally, it would have been obvious to design antisense oligonucleotides comprising the various modifications recited in the instant claims, particularly wherein the claimed oligonucleotide comprising a chimeric structure including a stretch of deoxynucleotides flanked by 2'-O-methoxyethyl modifications, phosphorothioate internucleoside linkages, and 5-methylcytosines, since Bennett et al. clearly teach that oligonucleotides comprising this structure al. are disclosed as having increased nuclease stability and increased cellular uptake. Moreover, it would have been obvious to design compounds comprising locked nucleosides comprising a bridge between the 2'-O and the 4' carbon atom. Oligonucleotides comprising this modification are

described as forming duplexes with higher specificity with its target, and having increased thermostability with its target in comparison to un-modified oligonucleotides.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 46-47, and 68-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46, and those claims dependent thereon, recite the following:

46. (Previously Presented) The compound of claim 1, wherein said compound is an, antisense oligonucleotide comprising the nucleobase sequence of SEQ ID NO: 19, wherein said antisense oligonucleotide comprises a ten deoxynucleotide region flanked on both the 5' and the 3' ends with at least five 2'-O-(2-methoxyethyl) nucleotides, wherein each internucleoside linkage in said antisense oligonucleotide is a phosphorothioate and wherein each cytosine in said antisense oligonucleotide is a 5'-methylcytosine.

The metes and bounds of this compound are vague and indefinite since it is unclear if the "ten deoxynucleotide region flanked on both the 5' and 3' ends" of the antisense oligonucleotide are encompassed within the original nucleotide sequence

recited in the compound of claim 1, or are these sequences in addition to the nucleotides of the compound of claim 1.

Claim 68 recites the following:

68. (Previously Presented) The compound of claim 67, wherein said compound comprises:
a region of deoxynucleotides flanked on both the 5' and the 3' ends of said region with at least one 2'-O-(2-methoxyethyl) nucleotide;
wherein each internucleoside linkages of said compound is a phosphorothioate internucleoside linkage;
and wherein each cytosine of said compound is a 5-methylcytosine.

The metes and bounds of the phrase "a region of deoxynucleotides flanked on both the 5' and the 3' ends of *said region*.," since it is unclear which "region" applicants are referring to, the "region of the deoxynucleotides" or the "region" with respect to the compound of claim 67. It is noted that claim 73 recites the same phrase, "a region of deoxynucleotides flanked on both the 5' and the 3' ends of *said region*.," therefore claim 74 is rejected for the same reasons.

Claims 70-72 recite the phrase"said modified oligonucleotide consists of a ten deoxynucleotide region flanked on both the 5' and the 3' ends with five 2'-O-(2-methoxyethyl) nucleotides." This phrase is vague and indefinite since it is unclear if the ten deoxynucleotide region is in added to the "5' and the 3' *ends* " of the oligonucleotide, or if the first five nucleotides of the oligonucleotide and the last five nucleotides at the 5' and 3' ends of the oligonucleotide comprise 2'-O-(2-methoxyethyl) nucleotides.

20. Claims 46-47, and 69-72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the

limitations of the base claim and any intervening claims, and further rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

21. Claims 62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1, 4-7, 9, 13, 20-23, 46-47, 50, 52-62, and 66-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-51, 57, 74, 82-83, 89, and 94-120 of copending Application No. 10/547,239. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the instant claims are drawn to compounds of 12 to 50 oligonucleotides in length that comprise an at least 8-nucleobase portion of SEQ ID NO: 19 and is at least 95 complementary to SEQ ID NO: 4. SEQ ID NO: 19 of the instant claims targets nucleobases 332 through 351 of SEQ ID NO: 4, the claims of the copending application are drawn to compounds of 12 to 50 targeting nucleotides 290-369 of SEQ ID NO: 4, moreover, the copending claims are also drawn to compounds 95% or fully complementary to nucleotides 332 to 356 of SEQ ID NO: 4. The scope of the instant claims clearly represent a species of the broad genus of compounds recited in the copending application, and thus anticipate the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633